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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,013	09/13/2005	Peter Muhlradt	03100220AA	5050

30743 7590 02/08/2007

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EXAMINER	
HA, JULIE	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,013	MUHLRADT ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-10* is/are rejected.

7)☐ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 03/11/05
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *January 12, 2007*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment filed on December 12, 2006 is acknowledged. Claims 1-10 are pending in this application.

Restriction

1. Applicant's election with traverse of the election of species of S-2,3-bis(acyloxy)-(2SorSR)-propyl]L-cysteinylcarboxypolyethyleneglycol and R1 and R2 residues may be identical or different and are C8-C22 alkyl, alkeneyl or alkynyl groups, the residue is polyethylene glycol, Y is oxygen, and X is OR where R is hydrogen in the reply filed on December 12, 2006 is acknowledged. The election of immunostimulation for the use of the conjugate on January 12, 2007 is acknowledged. The traversal is on the ground(s) that the application is a national stage filing based on PCT application. The Applicants argue that at the international stage, all claims were considered as noted from the International Search Report. Thus, restriction of the invention to a particular species after all claims have been considered at the international stage appears to be improper. Furthermore, the Applicants argue that there is no undue burden on the Examiner since the claims have already been identified as being allowable in Europe. This is not found persuasive because US practice is different from International Practices. What may have been found allowable may not be found allowable at the National Stage. 37 CFR 1.141 states the following:

> (a) Two or more independent and distinct inventions may not be claimed in one national application, ex-cept that more than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims in

one national application, provided the application also includes an allowable claim gen-eric to all the claimed species and all the claims to species in excess of one are written in dependent form (§ 1.75) or otherwise include all the limitations of the generic claim.

(b) Where claims to all three categories, product, process of making, and process of use, are included in a national application, a three way requirement for restriction can only be made where the process of making is distinct from the product. If the process of making and the product are not distinct, the process of using may be joined with the claims directed to the product and the process of making the product even though a showing of distinctness between the product and process of using the product can be made.

Since the claims are drawn to a compound with many different variables that would render each compound distinct due to structural differences, thus, Species election is deemed proper. Additionally, claims 1-6 are drawn to a bisacyloxypropylcysteine conjugate, claims 7-9 are drawn to a pharmaceutical composition comprising a bisacyloxypropylcysteine conjugate, and claim 10 is drawn to the use of the bisacyloxypropylcysteine conjugate. Following 37 CFR 1.141(b), these have been considered as one invention.

The search for each of the inventions is not co-extensive particularly with regard to the literature search. Burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and

literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement, and double patenting issues. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application.

Furthermore, the Applicants have attached the claims deemed to be allowable in Europe. However, these are not considered because the Election of Species is deemed proper in the US practices.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-10 are pending in this application.

Statement about Information Data Sheet:

2. While the information has been considered, a line has been drawn through the PCT International Search Report, because the search report does not have a publication date report.

Objection-Specifications

3. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in

upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

4. The specification is objected to since there is no clear headings/divisions in the specification. The Applicants are advised to correct this error.

5. The specification is objected to since there is a spelling error on line 8. The word "lipoopeptides" should be corrected to "lipopeptides".

Objection-Claims

6. Claim 1 is objected to as being unclear. The claim is drawn to a bisacyloxypropylcysteine conjugate. It is unclear whether R_3 is just the 2 polyethylene glycol or more than that, since claim 1 reads "R_3 is a covalently, ionically or

associatively bonded conjugate radical, in particular a water-soluble and physiologically tolerated, covalently or ionically bonded polymer, in particular covalently bonded polyethylene glycol (polyoxyethylene), -(CH_2-CH_2-O)m-CH_2-CH_2-X". The Applicants are advised to revise the language in the claim.

Claims Rejection-35 U.S.C. § 112, 2nd

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention..

8. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "several radicals" imply there are at least 3 Rs. The dictionary meaning for several is "being more than two but fewer than many in number or kind". However, where X = OR, NR_2, SR, COOR, there are 1, 2, 1, 1 Rs, respectively. How can several radicals be different? It is unclear since R is not defined clearly.

Claims Rejection-35 U.S.C. § 112, 2nd and 101

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. A claim which recites "The use of" merely recites a use without any active, positive steps delimiting how this use is actually practiced. *Ex Parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). MPEP § 2173.05(q).

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claim 10 provides for the use of the bisacyloxypropylcysteine conjugates, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims Rejection-35 U.S.C. § 112, 1st

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-4 and 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

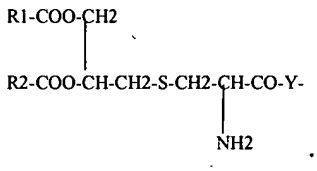
The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims 1-9 are drawn to a bisacyloxypropylcysteine conjugate according to formula (I) characterized by R_1, R_2, Y, R_3, X, and R. The generic

statement bisacyloxypropylcysteine conjugate does not provide ample written description for the compounds since the claim does not describe a single structural feature. For example, the variable R_3 contains multiple variabilities. R_3 is a covalently, ionically or associatively bonded conjugate radical, in particular a water-soluble and physiologically tolerated, covalently or ionically bonded polymer, in particularly covalently bonded polyethylene glycol (polyoxyethylene) and), -(CH_2-CH_2-O)m-CH_2-CH_2-X. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 1 is broad generic with respect to all possible compounds encompassed by the claim. The possible structural variations are limitless to any class of peptide or a peptide-like molecule, any water-soluble polymer molecules, and peptide, peptide-like molecules, and small molecules. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since

the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a water-soluble polymers. The specification is limited to polyethylene glycol (polyoxyethylene) and -(CH_2-CH_2-O)m-CH_2-CH_2-X when claim is covalently, ionically or associatively bonded conjugate radical. The specification is limited to the S-[2,3-bis(palmitoyloxy)-(2S)-propyl]-L-cysteinyl-carboxypolyethylene glycol and S-[2,3-bis(palmitoyloxy)-(2R)-propyl]-L-cysteinylcarboxy-polyethylene glycol. Many structural differences are possible due to different variables, however, the specification does not provide sufficient examples. Furthermore, claim 1 recites that the



polymeric radical R_3 is substituted once, twice or several times by . There are 4 different reaction locations, R_1, R_2, NH_2, and Y. The specification does not disclose where the polymeric radical reaction location is and how it is associated. The specification does not further disclose where the fatty acid in bisacyloxypropylcysteine is required to have fatty acids. Additionally, claim 2 recites alkyl, alkenyl and alkynyl fatty acids. The specification does not disclose these fatty acid radicals except the two mentioned above.

The specification does not describe any water-soluble polymer radical except that it is selected from 100 to 30000 daltons per bisacyloxypropylcysteine molecule and in the case of polyethylene glycol, a chain length m of from 5 to 700, preferably of from 100 to 500. The specification gives a working example and describes bispalmitoyloxypropylcysteine-PEG (BPP-Cys-PEG) and bisacyloxypropylcysteine

(BAP-Cys-PEG) (see paragraphs [0050] and [0053]). There are many varieties of palmitoylated and acylated derivatives, such as acylated derivatives of S-(2,3-dihydroxypropyl)-cysteine (see Metzger et al, Int. J. Peptide Protein Res., 1991, 545-554).

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

15. Claim 10 is rejected are under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the

predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to a bisacyloxypropylcysteine conjugates and the use of the conjugates for stimulating macrophages, for stimulating antibody synthesis, for defense against infection, for immuno stimulating, for treatment in connection with tumors, for preventing septic shock, for treating septic chock, for wound healing, or for use as an adjuvant for vaccines.

(2) The state of the prior art:

While enabled for stimulating macrophages, for stimulating antibody synthesis, for treatment in connection with tumors and adjuvant for vaccines, the Invention is not enabled for defense against infection, for preventing septic shock and treating septic shock and for wound healing.

The Merck index indicates that septic shock and sepsis are caused by hospital-acquired gram-negative bacilli or gram positive cocci and often occur in immunocompromised patients and those with chronic and debilitating diseases. Additionally, septic shock occurs most often in neonates, patients > 35 years old and

pregnant women. Predisposing factors include diabetes mellitus, cirrhosis, leukopenia associated with cancer or treatment with cytotoxic drugs. Common causative sites of infection include the lungs and the urinary, biliary, and GI tracts. The Merck index further indicates that the pathogenesis of septic shock is not completely understood (see Merck Index, Etiology and Pathophysiology).

Additionally, the use of conjugate for defense against infection is interpreted as "vaccine against infection". Vaccines can be prophylactic or therapeutic. As taught in virology courses and text books, one virus/bug infects the host cell. There is no way to prevent infection of the host cells. The thing that is being prevented is the symptoms of the infection.

Hoffmann et al (Immunobiol, 1988, 177: 158-170) teaches that synthetic lipoproteins Pam3-Cys-Ser-Ser-Asn-Ala and Pam3-Cys-Ser from E. coli as well as lipoprotein form other Enterobacteriaceae constitute potent polyclonal B lymphocyte activators (see abstract). Pam3Cys-Ser as well as Pam3Cys-Ser-Ser-Asn-Ala was able to stimulate Balb/c B lymphocytes to proliferate and differentiate into immunoglobulin producing cells (see p. 162). Additionally the reference teaches that adherent cells seem to play a role not only in inducing lymphocyte activation by the production of IL1, but also in modulating the immune response by the release of a variety of mediators, e.g. prostaglandins (see p. 166). Furthermore, the reference indicates that the molecular mechanism of macrophage and B cell activation by the lipopeptides is still unknown. In previous studies, it was demonstrated the binding of lipoprotein and lipopeptides to defined membrane proteins of B lymphocytes, which include proteins of

the major histocompatability complex, but it is still not known which of these binding proteins, if any, are responsible for the transduction of the stimulatory signal (see p. 168).

Muller et al (Immunology, 2001, 103: 49-60) indicate that synthetic lipopeptides derived from bacterial lipoprotein, such as P3CSK4 has been shown to be an effective immunoadjuvant in parenteral, nasal and oral immunization. In vitro P3CSK4 constitutes a potent macrophage/monocyte activator resulting in the induction of lymphokine production, phagocytosis, activation for tumor cytotoxicity, tumor necrosis factor-a production and release of reactive oxygen and nitrogen intermediates (see page 55, 1st paragraph of Discussion).

Esche et al (Int J Immunopharm, 2000, 22: 1093-1102) indicate that P3CSK4 constitutes an effective adjuvant for DNA immunizations, especially increasing weak humoral immune responses (see abstract). The reference teaches administration of DNA in mice, and specific antibodies were monitored by ELISA (see page 1096).

Raghow R (FASEB J, 1994, 8: 823-831) indicates that wound healing involves vast and elaborate interactions among the fibroblastic, endothelial, and epithelial cells, and the cells of the immune system. Furthermore, extracellular matrix (ECM) in addition to being a direct modulator of cellular phenotype, may also be a critical determinant in spatially restricting the availability of potent cytokines at the site of inflammation and healing (see p. 824, left column). The reference also teaches that there are important gaps in understanding of the molecular mechanisms by which enhanced biosynthetic

activities, proliferation, and phenotypic transformation of the key cells engaged in the repair process, and the synthesis and reorganization of ECM (see p. 830, Perspective).

The art provide guidance as how the synthetic lipopeptides are potent stimulators for human monocytes and murine macrophage, stimulates antibody synthesis, immunostimulators, and adjuvant for vaccines. The prior art discussed above also indicates wound healing mechanism is complex and elaborate interactions among the fibroblastic, endothelial, and epithelial cells, and the cells of the immune system. However, none of the prior arts provide guidance as how to determine individuals who are susceptible to infection and septic shock.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determination of predicting those who are susceptible to infection, septic shock, and wounds. Since the activity is based on determining the patient population that is susceptible to infection, septic shock, and wounds, the predictability in the art is low. This is due to the fact that the art has recognized the difficulty in determining the patient population who are susceptible to infection, septic shock, tumors, and wounds.

Annane et al (JAMA, 2000, 283(8): 1038-1045) teach that the hypothalamic-pituitary-adrenal axis is a major determinant of the host response to stress. However,

the relationship between its activation and patient outcome is not known. The reference teaches that there are several clinical prognostic factors, such as preexisting underlying disease, presence of organ dysfunction, and severity of illness scores, and hormonal profile to predict the outcome in critically ill patients. However, a pathophysiologic derangement that could help identify a group of patients who might benefit from a particular treatment has not been characterized (see p. 1038).

Parrillo JE (NEJM, 1993, 328(20): 1471-1478) teaches that mortality (in patients with septic shock) is related to the severity of both the sepsis and the underlying disorder that is nearly always present. The manifestations of sepsis include those related to the systemic response to infection (tachycardia, tachypnea, alterations in temperature, and leukocytosis) and those related to organ-system dysfunction (cardiovascular, respiratory, renal, hepatic, and hematologic abnormalities). Sepsis is one example of a systemic inflammatory response that can be triggered not only by infections by also by noninfectious disorder, such as trauma. The reference also teaches the associations confers a poorer prognosis but are not precise enough to predict the outcome in and individual patient (see p. 1471, 2nd paragraph).

The claim doesn't identify the patient population, therefore, the claim implies that anyone can be protected against septic shock, infection, and treated for tumors, septic shock and wound healing. However, the Applicant has not shown who will be susceptible to septic shock and infection. There are too many variables between the patient populations, thus, it clearly shows the unpredictability of the art.

(5) The breadth of the claims:

The claims are drawn to a bisacyloxypropylcysteine conjugate according to formula (I) and the use of the bisacyloxypropylcysteine conjugates for stimulating macrophages, for stimulating antibody synthesis, for defense against infection, for immuno stimulating, for treatment in connection with tumors, for preventing septic shock, for treating septic chock, for wound healing, or for use as an adjuvant for vaccines.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

Although the specification provides guidance on how to measure the biological activation of macrophage in vitro, wound healing in diabetic mice, eliciting an effective humoral response at systemic and mucosal levels, and effective T cell-mediated proliferation response, it is unclear as to when to administer the compound, other wounds and the patient population. The specification discloses that in a diabetic mice, an area approximately 4 x 4 cm was shaved on the back and depilated, and disinfected with Braunol. After anesthesia had been applied, the skin was defatted and cut out and 3 x 200 kUnits of compound were administered. The working example is limited to patients who are diabetic and the surface, epidermal wounds that have been disinfected. The working example also discloses to determine the total IgA in the lung and vagina washings, serial dilutions of corresponding samples were incubated in microtiter plates with the plates having been previously coated with goat anti-mouse

IgA. Additionally, to elucidate the effective T cell-mediated proliferation response, spleens were removed, cells propagated and plated on microtiter plates. Proliferating cells was determined using a scintillation counter. There are not enough working examples for guidance. For example, as explained above, a pathophysiologic derangement that could help identify a group of patients who might benefit from a particular treatment has not been characterized (see Annane et al, p. 1038). Parrillo JE (NEJM, 1993, 328(20): 1471-1478) teaches that sepsis is one example of a systemic inflammatory response that can be triggered not only by infections by also by noninfectious disorder, such as trauma. The reference also teaches the associations confers a poorer prognosis but are not precise enough to predict the outcome in and individual patient (see p. 1471, 2nd paragraph).

Additionally, Harris et al (Clin Pharmacokinet 2001, 40(7):539-551), Veronese FM (Biomaterials, 2001, 22: 405-417) and Roberts et al (Advanced Drug Delivery Reviews, 2002, 54: 459-476) teach problems and solutions of peptide and protein PEGylation. Harris et al teach that pegylation increases the size and molecular weight of a molecule. It also produces alterations in the physicochemical properties of the parent molecule. These include changes in conformation, steric hindrance, changes in electrostatic binding properties, hydrophobicity, local lysine basicity and pI. These changes can influence the binding affinity of the therapeutic protein to cellular receptors, resulting in changes in the bioactivity of the agent (see p. 543, 3. Effect of Pegylation...). Veronese FM indicates that the same mechanism that prevents the approach of proteolytic enzymes of antibodies to PEGylated protein can also reject a

substrate from the protein active site (see p. 411). Furthermore, Roberts et al indicates that most pegylation chemistry is designed to create a conjugate that contains a stable linkage to the protein, and it is generally observed that stable linkages to a protein can reduce the activity, possibly due to the presence of the PEG chain at the active or binding site of the protein or steric crowding at the active or binding site (see pp. 467-468). Furthermore, Harris et al teach that pegylation forms a protective 'shell' around the protein. This shell and its associated waters of hydration shield the protein from immunogenic recognition and increase resistance to degradation by proteolytic enzymes (see p. 543, third paragraph). If this is the situation, how can the Applicants be sure that the conjugates can immuno stimulate? The pegylated conjugates may present problems for immuno stimulation.

Additionally, Raghow indicates that there are important gaps in our understanding of the molecular mechanisms by which the enhanced biosynthetic activities, proliferation, and phenotypic transformation of the key cells engaged in the repair process, and the synthesis and reorganization of ECM. Raghow indicates TGF-b as a major player in the repair processes (see p.830, 2nd paragraph of Perspective). Kim WJH (Yonsei Medical Journal, 2000, 41(6): 692-703) indicates tissue regeneration is a complex cellular process, which includes the processes of inflammation, angiogenesis, extracellular matrix synthesis, reepithelialization and collagen deposition. The complexity and clinical variability of wound healing has limited pharmacologic approaches to accelerate wound repair (see p. 692, right column, 2nd paragraph).

The specification has not provided guidance in the way of a disclosure to how to determine individuals that need protection against septic shock and infection and treatment for tumors, septic shock and wound healing. The specification discloses that the invention is particularly suited for wounds on diabetic patients. Applicant's activity is on the premises of bisacyloxypropylcysteine conjugates acting as macrophage activators. However, as indicated by prior arts, identifying the group of patients who are prone to septic shock who might benefit from a particular treatment has not been characterized. The Merck index indicates that septic shock and sepsis are caused by hospital-acquired gram-negative bacilli or gram positive cocci and often occur in immunocompromised patients and those with chronic and debilitating diseases. Additionally, septic shock occurs most often in neonates, patients > 35 years old and pregnant women. Predisposing factors include diabetes mellitus, cirrhosis, leukopenia associated with cancer or treatment with cytotoxic drugs. Common causative sites of infection include the lungs and the urinary, biliary, and GI tracts. The Merck index further indicates that the pathogenesis of septic shock is not completely understood (see Merck Index, Etiology and Pathophysiology). The underlying mechanism is also unclear as what causes septic shock, since Parrillo teaches that sepsis is one example of a systemic inflammatory response that can be triggered not only by infections by also by noninfectious disorder, such as trauma. Furthermore, if the patient population is unknown, how can the Applicant know that a macrophage activator will work?

There is no clear guidance as to how to determine the patient population, since not all clinical patients are prone to septic shock, not all diabetics are prone to wounds

and not every infection leads to infection as described above. Since the prior art is still unclear as to who are susceptible to septic shock, infection, wounds and tumors, more guidance is necessary.

(8) The quantity of experimentation necessary:

Since it is uncertain to predict the patient population who are susceptible for septic shock, infection, wounds and tumors, and the Applicant have not provided the appropriate time frame at which the compound should be administered, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the bisacyloxycysteine conjugates are effective in treating patients of septic shock, infection, wounds and tumors.

Conclusions

17. Claims 5 and 6 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Peptide of claims 1, 5 and 6 are found free of the prior art because the prior art does not anticipate or render obvious instant invention. In the instant claims, Y has to be –NH-, -O-, -S-, or –OCO-. The closest prior art (Tam JP, US Patent # 5580563) consists of 3 palmitoyl groups (see Figure 14). Other prior arts require Y to be a peptide. For example, in Hoffmann et al (Immunobiol, 1988, 177: 158-170) Y is Cys-Ser-Ser-Asn-Ala (see p. 161); in Muehlradt PF (US Patent

6573242), Y is a peptide consisting of SEQ ID NO: 1 (see column 1, lines 42-45). Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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